COMIRB Protocol
COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
CAMPUS BOX F-490 TELEPHONE: 303-724-1055 Fax: 303-724-0990

COMIRB Record #: 16-2621
Protocol #: PCORI (154219) AD-1511-33395
Project Title: A Stepped Care Intervention to Reduce Disparities in Mental Health Services among Underserved Lung and Head-and-Neck Cancer Patients and their Caregivers
Principal Investigator: Evelinn A. Borrayo, PhD
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I. Hypotheses & Specific Aims: Medically underserved (i.e., low-income, uninsured, underinsured) cancer patients and their caregivers generally experience disparities in accessing mental health services. We will adapt evidence-based strategies to a *stepped-care intervention* model to address the mental health needs of underserved lung cancer (LC) and head-and-neck cancer (HNC) patients and of their caregivers across levels of depression and anxiety symptoms (e.g., mild, moderate, severe symptoms). We will compare the *stepped-care intervention* to "usual care," which will be *enhanced usual care* (standardized list of mental health resources) due to variability in usual care offered across hospitals. We aim to recruit 848 underserved patients and 848 of their caregivers (1,696 participants) who will be screened to be randomized to a clinical trial. We estimate that about 816 participants (47%-57%) will not meet randomization criteria, leaving about 222 LC and HNC patients and 222 of their caregivers to be randomized to 1-of-2 arms. A randomized controlled trial (RCT) will compare the effectiveness of the *stepped care intervention* versus an *enhanced usual care* condition on reducing emotional distress and improving coping skills among medically underserved LC and HNC patients and their caregivers.

Specific Aim 1: To work collaboratively with our clinician, patient and caregiver stakeholders to develop and implement a study protocol to ensure standardization of methods, fidelity of the intervention and its integration with clinical care.

Specific Aim 2: To adapt the *stepped-care intervention* and *enhanced usual care* to ensure strategies, delivery, and assessments are sensitive to participants' characteristics and properly applied, monitored, and integrated with clinical care.

Specific Aim 3: To conduct a randomized controlled trial to assess if the *stepped care intervention* improves the primary patient-centered outcomes (depression and anxiety symptoms; coping skills) compared to an *enhanced usual care* condition.

Hypothesis 1 (patients): Patients in the intervention group will show improvements in distress (depression and anxiety) and on coping self-efficacy compared to those in the usual care group. However, we hypothesize that QoL and perceived stress will remain similar across groups, indicating the intervention mitigates distress and coping in spite of treatment-related stress and decreased QoL.

Hypothesis 2 (caregivers): Caregivers in the intervention group will show improvements in distress (depression and anxiety) and on adaptive coping compared to those in the enhanced usual care group. However, we hypothesize that caregiver burden and perceived stress will remain similar across groups, indicating that the intervention mitigates distress and coping in spite of caregiving stress and burden.

II. Background and Significance

LC is the primary cause of cancer death among men and women in the United States.[1] A significant number of LC patients present also with a primary diagnosis of head-and-neck cancer (HNC) or due to heavy smoking are at risk of developing these cancers and vice versa.[2, 3] LC and HNC are considered among the most "traumatic" forms of cancer.[6] Treatment via surgery, radiation, and chemotherapy affect the most basic functions of life (e.g., breathing, swallowing, speaking, smell, taste, and vision).[7] Physical disfigurement, weight loss, and high levels of pain and discomfort[8-10] result in poor quality of life (QoL)[4, 8, 11-18] and high psychological distress related to high levels of pain, treatment side-effects, and self-image disturbances.[5, 18] LC and HNC patients tend to experience high levels of anxiety (about 33% of LC patients),[19] which increases as side effects increase and physical functioning decreases.[19-22] As a result, LC and HNC patients tend to experience higher suicidality than other cancer patients.[15, 23]

Social support tends to be lower among LC and HNC patients due to stigmatization,[24-31] functional disability, and physical disfigurement,[32-35] which often results in greater psychological distress.[36-38] The main source of social support for LC and HNC patients is often their caregivers.[39, 40] Unfortunately, caregivers' needs and distress often goes unrecognized.[41] Similar to LC and HNC patients, distress in caregivers has been found to diminish their functioning, and consequently the quantity of home care they provide to patients.[42] Caregivers are also affected by higher physical morbidity and premature mortality.[43, 44] Additionally, caregiver burden has been significantly associated with higher anxiety and depressive symptoms[47-49] and with significantly lower QoL among caregivers.[45, 46, 50-52]

There is limited research on the use of psychological interventions tailored to caregivers of LC and HNC patients, as well as on psychological interventions that include both caregivers and patients. There is also a void in the research on psychological interventions with medically underserved LC and HNC patients. Medically underserved cancer patients are significantly more likely to experience worse distress, higher levels of clinical depression, and lower QoL compared to other cancer patients.[55] There is a need for studies that assess whether underserved LC and HNC patients and their caregivers benefit from evidence-based treatment to decrease psychological distress and improve their functioning.

III. Preliminary Studies/Progress Report:

In a pilot study, the PI, Dr. Borrayo et al. (2016),[56] explored the challenges that underserved LC and HNC Hispanic patients undergoing treatment and their caregivers encountered. There were 40 medical charts reviewed and 29 participants were interviewed, including 4 LC patients, 5 HNC patients, 6 caregivers, 7 health care providers, and 7 lay-health workers about the treatment challenges that low-income patients and their caregivers experienced that contribute to treatment delays. The mental health challenges (i.e., depression, anxiety, substance abuse, fear) were reported to be the most concerning and to have negatively affected patients' QoL and their treatment adherence, further contributing to treatment delays. Health care providers also expressed concern about patients' lack of access to mental health care to address emotional and behavioral challenges.

In a previous pilot study, Dr. Kilbourn et al. (2013) assessed the acceptability and feasibility of an evidence-based intervention [i.e., "Easing and Alleviating Symptoms during Treatment" (EASE)] with 24 HNC patients (34% attrition) to improve symptom management, distress, coping, and QoL among HNC patients.[57] The intervention delivered evidence-based CBT and stress management across eight telephone counseling sessions.[58] The CBT intervention was found acceptable, feasible, and clinically relevant to HNC patients. Dr. Kilbourn et al (2011) administered the same EASE intervention to caregivers of hospice patients in the Caregiver Life Line project (N = 19). In this pilot study.[59] The CBT intervention included up to 12 weekly telephone calls aimed at fostering adaptive coping skills in the

caregivers. Caregivers were assessed at baseline, 3 months and 6 months for depression, emotional QoL, perceived stress, social support and benefit finding. Results demonstrated a trend toward reduced symptoms of depression and increased emotional QoL (greater reduction at 6 months than at 3 months, suggesting that the benefits of participating in the intervention may become more apparent over time). Caregivers reported high levels of self-efficacy regarding their ability to implement the coping skills learned. These findings demonstrate that the EASE's CBT stress-management intervention is acceptable, feasible and beneficial to caregivers. Based on this evidence, the next step is to conduct a rigorous RCTs to assess whether evidence-based CBT stress-management interventions are equally effective at improving mental health outcomes among underserved LC and HNC patients and caregivers.

IV. Research Methods

A. Outcome Measures: We will utilize patient-reported outcome (PRO) measures that have been found to be valid and reliable, including with Spanish-speaking populations (see Table 1). To ensure that the measures are appropriate for low-literacy populations, a pilot test was conducted with our patient and caregiver stakeholders and items that were difficult to understand or to answer were simplified. Thus, we will further assess their validity and reliability in our sample. All consented study participants will be compensated $25 to complete the measures at baseline ("baseline measures"), which will also include sociodemographic questions to determine "randomization inclusion and exclusion criteria." Only participants who are randomized to condition will complete the measures at 6-weeks, 3-months and 6-months from the date they completed the baseline measures and will be compensated $25 every time.

Table 1. Patient-centered outcomes to be assessed at baseline, 6-weeks, 3-months, and 6-months

	Patients	Caregivers
PRIMARY OUTCOMES		
Depression & Anxiety	Hospital Anxiety and Depression Scale (14 items)	Hospital Anxiety and Depression Scale (14 items)
Depression	PROMIS-Ca Form v1.0 – Depression (30 items)	PROMIS Form v1.0 – Depression (28 items)
Anxiety	PROMIS-Ca Form v1.0– Anxiety (22 items)	PROMIS Form v1.0 – Anxiety (29 items)
Coping	Coping Self-Efficacy (26 items)	Coping Self-Efficacy (26 items)
SECONDARY OUTCOMES		
Health-Related Quality of Life	FACT-Lung Cancer version 4 (36 items)	
	FACT-Head-and-Neck Cancer (27 items)	
Perceived Stress	Perceived Stress Scale (PSS) (10 items)	Perceived Stress Scale (PSS) (10 items)
Caregiving Burden		Zarit Burden Interview (ZBI) (12 items)

The measures package takes about +/- 30 minutes to complete when it is *self-administered online* or via a *hard copy* but about 45 minutes when administered orally in person or over the phone. If a participant is unable to complete the measures online or express preference for a hard copy, they will be:

(1) Mailed a copy of the measures and ask to return within 15 days of receipt. If after 15 days of the initial online request or if they expressed preference for an oral administration, they will:
(2) Receive a phone call from a Graduate research assistants (GRA) who will administer the measure to participants by phone. If the GRAs are unable to locate the participants after 3 attempts (including leaving voice messages), they will
(3) Alert the Site Research Coordinators who will approach the participants to administer the measures in person either electronically with an iPad or with a hard copy.

The following outcomes will be measured at baseline, 6-weeks, 3-months and 6-months:

<u>Distress (depression and anxiety symptoms)</u>: We will use two measure of distress. First, the 14-item Hospital Anxiety and Depression Scale (HADS) will be administered at baseline to obtain a global measure of anxiety (HADS-A) and depression (HADS-D) to provide validity data for the primary outcomes

to use in the study. The Cronbach's alpha for HADS-A has been reported from .68 to .93 (mean .83) and for the HADS-D from .67 to .90 (mean .82).[96] Second, we will use the Patient-Reported Outcomes Measurement Information System (PROMIS) measures will assess the primary outcomes of distress (depression and anxiety symptoms) in patients (PROMIS cancer version) and in caregivers (PROMIS adult version).[63] PROMIS measures have calibrated items (well-defined and validated) that have been found to be reliable measures.[65-67] Depression and anxiety symptoms constitute the primary study outcomes and will be interpreted as: (1) asymptomatic, *PROMIS score < 50;* (2) mild distress, *PROMIS score 50-59;* (3) moderate distress, *PROMIS score 60-69;* and (2) severe distress, *PROMIS score >70*. A *negative outcome* will include (a) unchanged distress scores or (b) an increase in distress scores at assessment points. A *positive outcome* will be a clinically significant decrease in distress at assessment points.

Coping Self-Efficacy: Coping Self-Efficacy (CSE) scale by Chesney et al. (2006)[73] assesses patient's confidence in their ability to choose and implement a successful coping strategy via 26 items rated from 1 to 10. The CSE taps into *problem-focused coping, stopping unpleasant emotions and thoughts,* and *getting support from friends and family,* all similar to emotion-focused coping, problem-focused coping, and social support of the CBT intervention. Internal consistency range from .80 to .91[73]

Health-related Quality of Life: We will use the Functional Assessment of Cancer Therapy (FACT)[76] to measure health related quality of life. The FACT has been found valid and reliable among lung cancer (FACT-L, *a*=0.68-89)[77,78] and head-and-neck (FACT-HN, *a*=0.74-86) patients.[83, 84] The FACT-L and FACT-HN incorporate the FACT plus additional symptom-specific items for LC and HNC. Items are rated on a 0 to 4 Likert type scale, and then combined to produce subscale scores and a global QoL score.

Perceived Stress: The Perceived Stress Scale (PSS)[81] will be used to measure *perceived stress*. This 10-item scale is scored on a 5-point Likert type scale to assess the degree to which situations are appraised as stressful. The PSS' internal consistency reliability range from 0.80 to 0.89[82] and has been used among cancer patients[83] and among caregivers of cancer patients.[84]

Caregiver Burden: The Zarit Burden Interview (ZBI) will measure caregiving burden. The 12 items ask caregivers to rate the impact that the patient's condition has had on the caregiver's life on a 5-point Likert-type scale. It provides an overall caregiver burden score, with higher scores indicating greater burden. The ZBI has good internal consistency reliability, with a Cronbach's alpha coefficient of .92.

Sociodemographic Characteristics at Baseline (including randomization inclusion and exclusion criteria): Demographic characteristics (not in Table 1) will be assessed at baseline with a self-report survey that includes participants' age, sex, place of birth, years living in the U.S., marital status, current and future employment status, education, and mental health history. For patients it will also include diagnosis and treatment questions, and for caregivers it will include questions about caregiving responsibilities. The survey will ask "randomization inclusion or exclusion criteria" questions to determine RCT eligibility:

1. *Questions related to inclusion criteria* will ask participants to report (a) what language they speak and read; (b) monthly income (after taxes); (c) how many people live at home that depend on the income reported; (d) health insurance status, including insurance type; and (e) estimated health insurance copays and deductibles (to estimate out-of-pocket costs).
2. *Questions related to exclusion criteria* will ask participants to self-report (a) current or past impairments (cognitive and affective disorders) that make participants vulnerable to decision-challenges; (b) current suicidal ideation; and questions to assess if they belong to vulnerable populations (e.g., inmates, homeless, pregnant, deaf).

B. Description of the Methods to Enroll Participants in the Study

Participants will be recruited from four hospitals: the **Denver Health and Hospital Authority (DHHA)**, **University of Colorado Hospital** and **National Jewish Hospital (NJH)** in Denver, and **Saint Mary's Hospital and Medical Center (St. Mary's)** in Grand Junction. Each hospital will hire as their employee a Site Research Coordinator who will be trained to recruit and consent study participants (hospitals will cede to COMIRB's oversight of the research, including personnel training requirements).

1. We will pre-screen all cancer patients to identify recently diagnosed LC and HNC patients through various methods:
    a. Monthly audit of electronic medical records from all hospitals to identified patients diagnosed with LC or HNC within 30 days prior to the audit.
    b. Weekly attendance to cancer tumor boards to identify recently diagnosed patients.
    c. Daily review of clinic visits to identify all LC and HNC patients in the oncology clinic, ear-nose-and throat (ENT) clinic, and radiation oncology clinic/unit at each hospital.
    d. Recruitment flyers in English and Spanish will be used to advertise the study at each hospital site and via Social Media sites. The flyers instruct recently diagnosed LC or HNC patients and their caregivers to contact the Site Coordinator if interested in the study.
    e. All patients and caregivers who agree and consent to participate in the study will receive a follow-up letter. The letter will include information based on whether or not the participant is randomized to a study condition, and if the participant is randomized, then he/she will receive a letter based on the step to which he/she was randomized. The letters are as follows: a) Letter to participants not randomized to a study condition, b) Letter to participants in the control condition, c) Letter to participants randomized to Step 1 of the intervention, d) Letter to participants randomized to Step 2 of the intervention, e) Letter to participants randomized to Step 3 of the intervention, f) Letter to participants randomized to Step 4 of the intervention.
    f. Advertise the study via Social Media sites and instruct recently diagnosed LC or HNC patients and their caregivers to contact the Site Coordinator if interested in the study.

2. All recently diagnosed LC and HNC patients and their caregivers will be informed and invited to participate in the study following a series of procedures:
    a. Site Coordinator will arrange an information meeting with the patient (e.g., scheduled medical visit) to introduce and invite patient (and caregiver if present) to participate.
    b. If the patient's caregiver is not present, the Site Coordinator will ask for the patient's agreement to contact their caregiver via phone to invite them to participate in the study. The patient will be informed that "dyad" participation is not required but that only one or both of them can participate if desired.
    c. For caregivers absent at the time of the patient's recruitment, the Site Coordinator will arrange to meet the caregiver to inform and invite them to participate in the study.

3. We will consent all recently diagnosed LC and HNC patients who agree to participate in the study
    a. For patients and caregivers who agree to participate, the Site Coordinator will arrange a time to explain and sign the informed consent (IC). The time to conduct the IC process and sign the IC form could be during the initial recruitment meeting or at another subsequent time if that is more convenient for the patient and/or the caregiver.

b. Participants will be provided with an electronic IC form to sign and will receive a hard copy for their records. The IC form and the oral explanation will emphasize that participants will (1) provide baseline data to determine if they meet the inclusion criteria to be randomized to 1 of 2 study conditions; (2) be randomized based on the "randomization inclusion and exclusion criteria" to either condition; and (3) participants who do not meet the randomization inclusion criteria will consent to remain in the study for comparison purposes (using only their unidentified baseline data).
c. Patients who do not agree or who are unsure about participating at the initial meeting will be instructed to contact the Site Coordinator (within a month of the initial meeting) if they change their mind and would like to participate in the study at a later date.
d. All patients and caregivers who agree and consent to participate in the study will complete "baseline measures" and will receive a $25 incentive. Sociodemographic questions will also include assessment of participants "randomization inclusion and exclusion criteria" criteria status to be further randomized to study condition.

Authorization Procedures

The protocol will be compliant with current HIPAA regulations and guidelines as follows:

A. Authorization (via informed consent) will be obtained by each of the hospital's Site Research Coordinator in a private and comfortable medical consultation room per site.
B. Potential participants will electronically sign the authorization form via an I-pad, but will receive a paper copy for their records that is unsigned (but they can request a signed copy).
C. The collection and use of each participant's protected health information (PHI) will be protected in REDCap™. We will not keep any PHI from our participants in paper form.
D. PHI for each participant will be kept unidentified in REDCap,™ to be identified by a numeric study code assigned to the participant upon being consented into the study (only the Site Coordinators as employees of the institutions will have access to identified information). The SRC will only record PHI on the diagnostic criteria (e.g., LC and HNC) from all pre-screened individuals. The SRC will also record demographic data (e.g.. age, gender, ethnicity, patient) to log recruitment efforts and for the DSMB to evaluate bias in recruitment, and for final analysis to determine demographics of individuals who were not included in the study.
E. Each participant will be asked to provide, if possible, two phone numbers to deliver to them information related to their participation in the study (e.g., appointment reminders).

4. Using information collected from the "baseline measures" we will screen for "randomization inclusion and exclusion criteria," which includes the following criteria:

LC and HNC patients' randomization criteria [*information in brackets refers to the question numbers that assess inclusion and exclusion criteria in the sociodemographic survey, attached*]

Eligibility criteria:

a) Recently diagnosed LC and/or HNC (within a month of recruitment date from the date of 1st visit oncology, ENT, or radiation clinic visit/consultation upon pathologic tissue diagnosis [*question #14*]
b) LC and/or HNC patients at any stage of diagnosis (Stages 0-IV) [*question #15*];
c) Over 18 years old; [*question #1*];
d) English and/or Spanish speaking [*questions #4*];
e) Medically underserved, as defined by at least one or several of the following:
    a. Low-income: Below 400% of the 2016 Federal poverty levels [85, 87] [*question #10*];

b. Uninsured: No health insurance (public or private insurance) [*question #9*];
c. Underinsured:
(c.1) Public insurance (e.g., Medicaid, Medicare exclusive, VA) [*question #9*];
(c.2) 10% of annual income on out-of-pocket medical expenses[86] for individuals below 200% of the 2016 Federal poverty levels [*questions #9 and #10].*

Exclusion criteria:

a) Individuals who do not meet eligibility criteria, including individuals who do not speak English or Spanish [at the discretion of the Site Coordinators upon recruitment];
b) Those who refuse treatment at one of four hospital sites.
c) Decisionally-challenged adults with cognitive or personality impairment [*question #19 & #20a-c*], suicidal ideation [*question #30*], or intoxication (alcohol or drugs) that might interfere with their ability to consent or participate in the study [at the discretion of the Site Coordinators upon recruitment or the Counselor during for the intervention];
d) Individuals from vulnerable populations (e.g., inmates [*question #29*], homeless [*question #28*], pregnant women [*question #2*], and those with auditory impairment [at the discretion of the Site Coordinators upon recruitment]). However, individuals who become pregnant or develop auditory impairments after they have been randomized to study condition may remain in the study until completion. Additionally, individuals on probation will be considered eligible and their participation in the study will not interfere with their requirements of probation.

<u>Caregivers of LC and/or HNC patients</u>

Eligibility criteria:

a) Primary caregiver of a recently diagnosed LC and/or HNC patient (per criteria for patients) [*question #13*];
b) Over 18 years old [*question #1*];
c) English and/or Spanish speaking [*questions #4 and #5*];
d) Medically underserved, as defined by at least one or several of the following:
    a. Low-income: Below 400% of the 2016 Federal poverty levels[85, 87] [*question #10*]
    b. Uninsured: No health insurance (public or private insurance) [*question #9*]
    c. Underinsured:
    (c.1) Public insurance (i.e., Medicaid, Medicare exclusive, VA) [*question #9*]
    (c.2) 10% of annual income spent on out-of-pocket medical expenses[86] for individuals below 200% of the 2016 Federal poverty levels [*question #9 and 10*].

Exclusion criteria:

a) Individuals who do not meet eligibility criteria, including individuals who do not speak English or Spanish [at the discretion of the Site Coordinators upon recruitment];
b) Caregivers of patients who refuse treatment at one of four hospital sites.
c) Decisionally-challenged adults with cognitive or personality impairment [*question #19 & #20a-c*], suicidal ideation [*question #30*], or intoxication (alcohol or drugs) that might interfere with their ability to consent or participate in the study [at the discretion of the Site Coordinators upon recruitment or the Counselor during the intervention];
d) Individuals from vulnerable populations (e.g., inmates [*question #29*], homeless [*question #28*], pregnant women [*question #2*], and those with auditory impairment [at the discretion of the Site Coordinators upon recruitment]). However, individuals who become pregnant or develop auditory impairments after they have been randomized to

study condition may remain in the study until completion. Additionally, individuals on probation will be considered eligible and their participation in the study will not interfere with their requirements of probation.

5. We will randomize participants (patients and caregivers) who meet the "eligibility criteria" and exclude from randomization participants based on the "exclusion criteria."

C. Randomized Controlled Trial (RCT) Design

Population: To estimate the population of participants, we obtained data on the number of patients who have been diagnosed with LC and HNC at DHHA, University of Colorado Hospital, NJH, and St. Mary's in a 3-year period (2012-2014) prior to the grant submission. The 4 sites had a population of about 1,211 LC and HNC patients who would be invited to participate in the study to complete "baseline measures," with about 70% of patients expected to meet criteria as being uninsured or underinsured patients. As **Figure 1** displays, the estimated sample is 848 patients (and 848 of their caregivers) expected to be eligible for randomization.

Participants who meet the "randomization inclusion criteria" will be randomized to condition by the database manager using the REDCap™ software at CU-Denver as follows:

1. Block randomization, adjusting for imbalance in patients' tumor site and stage of diagnosis in the analysis, will ensure an equal distribution of patients and caregivers across arms.
2. For patients and caregivers who both agree to participate in the study, they will be randomized together to the same condition (either "enhanced usual care" or "stepped-care intervention"). Per "baseline measures" of distress, patients and caregivers randomized to the "stepped-care intervention" will be assign to an intervention step based on their individual distress scores.

Randomization and sample size: **Figure 1** shows the participants' random assignment to study condition.

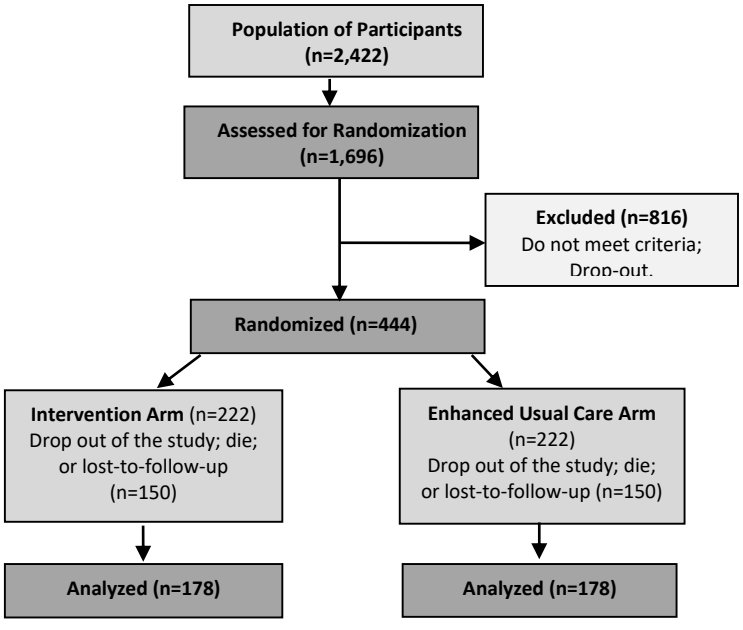

Figure 1. The 444 participants expected to be randomized (222 LC and HNC patients and 222 caregivers)

Of the 1,211 patients and 1,211 caregivers (2,422 participants) about 30% will refuse to participate, leaving 848 patients and 848 caregivers (n=1,696) to be screened for randomization. Of these, about 816 patients (47%-57%) will meet exclusion criteria) or refuse further participation (drop-out), based on average participation rates reported in other similar studies. [92] Thus, we estimate that about 444 participants (222 patients; 222 caregivers) will be randomized to one of 2-arms (or 222 per arm). About 44 participants in each arm might drop out of the study, have a member of the couple die, or be lost to follow-up (20% attrition), with 178 participants per arm to remain in the study for the analyses. **Figure 1 shows a total of about 356 participants will be available for final analyses.** This sample allows us to detect a 0.38 effect size with 90% power.

RCT Conditions/Arms

Arm 1: Enhanced Usual Care: DHHA, St. Mary's, University of Colorado Hospital, and NJH hospitals provide supportive mental health care for patients such as printed materials, support groups, crisis counseling, and specialized care (e.g., psychiatric medication). Because the amount of usual mental health care that each patient receives varies at each site, we will standardize and monitor the usual care arm across the four sites with an *enhanced usual care* condition. All participants will receive upon enrollment a "Mental Health Resource Guide" with, (a) web links with mental health resources available at the national and local level, and (b) a list of support groups and mental health care providers to access if they encounter challenges. Participants in the *baseline group* and *enhanced usual care*, per usual care practices, with high levels of distress, suicidal ideation and needing specialized care (e.g., psychiatric medication, crisis counseling), will be referred to specialized mental health care following the established protocol at the hospital rather than provided access to the intervention.

Arm 2: Stepped-Care Intervention: Our intervention strategies are grounded in evidence-based CBT, that include stress management and relaxation treatment strategies and coping skills training.[53, 58] Our treatment strategies have been adapted from the Transactional Model of Stress and Coping (TMSC), a theoretical model that predicts that individuals who are able to cope and adapt to the stress related to cancer treatment or caregiving will report less psychological distress than those unable to cope.[62] The TMSC will guide the progressive intensity of the treatment steps. The goal is to equip participants to identify and disaggregate the stress associated with treatment and caregiving related challenges (primary appraisal) while providing skills to manage stress, leading to increased adaptive coping (secondary appraisal), and reducing the emotional distress related to maladaptive coping.[58] We hypothesize that applying the CBT strategies[57, 59] in a *stepped-care intervention* format is likely to bring about the desired positive outcomes in distress levels.

Stepped-Care Intervention Steps: A Master's level Counselor will be hired as a hospital employee to only administer the intervention to participants (will not be involved in data collection). **Figure 1** describes the treatment steps that participants will be assigned to, based on their personal level of distress:[63]

Step 1: Watchful Waiting: (*PROMIS score < 50*).[63] A face-to-face *Orientation Session* will be conducted with all intervention participants with to establish therapeutic alliance and explain the purpose, design, and content of the intervention. Participants with no symptoms or with scores that fall below mild levels of distress will be followed by watchful waiting (active monitoring) only.

Step 2: Self-Help Guide: (*PROMIS score 50-59*).[63] Participants with mild levels of distress will receive the *Orientation Session* and a *Self-Help Guide*. The Guide will contain self-administered evidence-based stress-management and coping skills techniques[64, 54] that they can practice on their own. The Counselor will be available via telephone to answer questions about the Guide.

Step 3: Coping Skills Training: (*PROMIS score 60-69*).[63] Participants experiencing moderate levels of distress will receive the *Orientation Session*, the *Self-Help Guide*, and two *Coping Skills Training* sessions with the Counselor. Participants will learn problem-focused and emotion-focused coping strategies,[54] and to identify controllable and uncontrollable stressors and how to match them to the appropriate strategy. Participants will practice the strategies between sessions.

Step 4: Cognitive-Behavioral Therapy (CBT): (*PROMIS score >70*).[63] Participants reporting high levels of distress, will receive the *Orientation Session*, the *Self-Help Guide*, two *Coping Skills Training* sessions, and four *CBT sessions*. The Counselor will introduce evidence-based CBT techniques, which focus on modifying the impact of stress via the interpretation of and reactions to stressors (cognitive and emotional reactions) and by correcting cognitive distortions. Participants who are not helped by the intervention or who require specialized treatment will be referred for services at the hospital, although they will continue to be included in the final analyses. If a patient dies, the caregiver may continue participating and will be moved to Step 4 to receive a grief session.

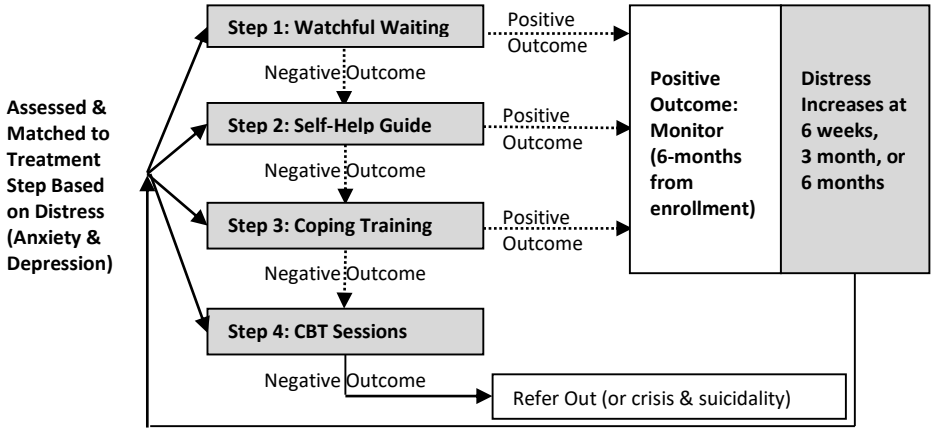

Figure 1. Stepped-Care Intervention Conceptual Framework to Assign Participants to a Step.[95]

Referral Protocol: Participants (*baseline group*, *enhanced usual care*, and *stepped-care intervention*) will be referred to specialized mental health care if they endorse suicide ideation or substance abuse items during any of the assessment points (baseline, 6-weeks, 3-months and 6-months) or if they voice such issues to the Site Research Coordinator upon enrollment or to the Counselor during the intervention. If participants are not helped by the intervention or require psychiatric medication, they will be referred also to specialized mental health services per protocols already in place at the participating hospitals. During the study's 12-hour training, the Site Coordinators and Counselors will be instructed to follow their institution's protocol for suicidal ideation and other crisis (e.g., intoxication) to make referrals.

D. Description, Risks and Justification of Procedures and Data Collection Tools

Potential Risks

a) Physical injury – No known risks, but if there are risks they are likely to be rare and the magnitude low.
b) Psychological trauma or stress – Psychosocial stress may increase in some participants during the intervention. Support will be given throughout the intervention or information about sources of support will be given in writing to ensure patient safety. It's magnitude, should it occur, would be minimal and likely to be short in duration.
c) Social/economic harm – No social or economic harm is anticipated. Time commitment to participate in the intervention and to answer the measures will be requested but not expected to result in social or economic harm.
d) Legal risk – No known risks, but if so they would be rare and the magnitude low.

e) Loss of confidentiality – Every effort will be made to maintain the confidentiality of participants by adhering to requirements for their protection that is in place by the institutions in the study.

Procedure for Protection against Risk

- All the investigators and staff will meet COMIRB's human subjects and institutional review board requirements.
- To minimize potential risks, the PI will monitor for any unanticipated problems while conducting the study and will report them to COMIRB.
- Research team meetings will be held once a month by the project's leaders with the research project's staff (e.g., Project Manager, Site Research Coordinators, Graduate Research Assistants) to closely monitor the study's implementation fidelity, progress, and proper and ethical conduct of the trial with human subjects.

Investigators/Institutions

No risk to investigators and study staff is expected.

Data Safety and Monitoring Board (DSMB): The DSMB will consist of four members who will have no direct involvement in the proposed project. The DSMB will meet twice a year with the research project investigators and with stakeholders during key points in the study's development, implementation, and evaluation to review its progress and provide feedback. If an adverse event (AE) occurs, the DSMB will be called for an emergency meeting and the AE will be reported to COMIRB, which oversees the project across institutions. Second, Dr. Borrayo and Dr. Kilbourn will hold monthly meetings with the research project's staff (e.g., Project Manager, Site Research Coordinators, Counselors, Research Assistants) to review and closely monitor the study's implementation fidelity and progress, including participants' recruitment and drop-out and any difficulties in collecting and processing the data. Minutes from the meetings will be used to record and track issues that need attention. Dr. Borrayo (PI) and Dr. Juárez-Colunga (biostatistician) will monitor the data monthly for consistency of collection. Upon enrollment of the first 15 dyads of patients and caregivers (5 from each site) and their subsequent completion of 6-months of participation, Dr. Juárez-Colunga will examine the data collected to assess if any problems exist.

Established mechanisms to ensure data safety: Study data will be stored in a database located on a secure password-protected, HIPAA compliant University server. The data will be entered electronically using wireless touch screen tablets into a coded database in REDCap™ that can only be accessed via password by authorized research personnel. The database is hosted at UCD|AMC Development and Informatics Service Center (DISC) and will be used as a central location for data processing and management. Access to the data will be based upon a unique username and password given to each user and stored within the REDCap authentication table. Users will need to be given rights to access the specific REDCap project database. Rights within the project will be given based upon the user's role in the project. For example, the SRC and Graduate Research Assistants (GRAs) would have rights to enter data, but will not have rights to electronically sign forms. A PI may be given rights to view data and electronically sign forms, but would not have rights to enter data. Users will be expected to comply with all applicable institutional policies regarding collection, storage, and analysis of data, including all applicable IRB and HIPAA regulations. Restricted access to the data will be handled via REDCap and only three team members will have access to the fill database: Dr. Elizabeth Juárez-Colunga (Co-I and statistician), 2) Data Manager (who will manage the database), 3) the Project Manager, and 4) Dr. Evelinn Borrayo (PI). Electronic communication about the data with outside research collaborators (e.g. Co-Investigators) and funding agency personnel (i.e. PCORI) will involve only unidentifiable information.

Intervention Counseling Sessions: Digital auto recordings containing confidential information about the participants will also be collected for protocol quality control and participants' safety monitoring. Counselors, employed by each of the hospitals, will deliver the intervention via in-person or over the phone and will audio record their counseling sessions with participants. Audio-recordings will be saved electronically with the numeric code used as the only identifier of the participant. The audio-recorded sessions will be reviewed by Dr. Kristin Kilbourn, Dr. Evelinn Borrayo, and Dr. Jeanette Waxmonsky, licensed clinical supervisors and IRB trained. The participants' names, last names, numeric study code, and contact information will be kept in our password-protected REDCap database. Audio-recordings will be shared electronically with the clinical supervisors, and with the PI and DSMB members HIPPA Compliant, University MS ONE Drive for Business account where they will be made accessible upon request.

E. Potential Benefits of the Proposed Research to Human Subjects and Others

To LC and HNC patients and their caregivers: Patients and caregivers who will receive the stepped-care intervention would benefit from receiving services that are targeted to their distress (i.e., mild, moderate, severe), which has the potential to improve their mental health wellbeing, along with potential gains in coping self-efficacy and decreased stress among other gains. Any risk involved in the study, such as temporary distress, may be outweighed by improvements to mental health needs.

To society: There is a dire need to provide underserved LC and HNC patients and their caregivers with mental health support. If successful, the intervention could improve mental health outcomes, patients and caregivers' satisfaction with care, QoL, and caregiver burden. It may also provide other institutions with a cost-effective method to help underserved cancer patients receive mental health treatment. Thus, information gained is likely to outweigh any minimal risks (e.g., temporary psychological distress).

Funding

PCORI (154219) AD-1511-33395. Funding of this study will not pay for medical or mental health treatment for the participants. Participants are responsible for their own standard medical or mental health care. Participants will be given a $25.00 compensation for taking the time to answer the measures during the four total assessment points, thus, each participant randomized to condition will be paid a total of $100. Participants who are not randomized will only answer the "baseline measures" and will only receive $25.00 for that assessment point. Participants will not be paid for participating in the study, the RCT, or the Counseling sessions provided through the stepped-care intervention.

Special Consent Issues

There are no consent issues involving special populations such as prison inmates, persons with cognitive disabilities, homeless, or minors.

Examinations, laboratory tests, and procedures

Not applicable

Biological Specimens/Genetic Testing

This study does not involve collection of specimens or genetic testing.

F. Potential Scientific Problems

Potential limitations to this study include: researcher bias, participants bias, and generalizability. However, the oversight of the development, implementation, and evaluation of the study protocol,

intervention, and conduct of RCT by a group of "Patient and Caregiver Stakeholders (PCS)," Clinician Stakeholders, and the DSMB will ensure that any bias introduce by the research team leadership and staff are minimized. The researchers will ensure that they standardize the interpretation of results during data analysis in order to reduce the impact of researcher bias. Some of our participants are cancer patients under distress and in need of services who might perceive the intervention to be more beneficial than under ordinary circumstances. Self-report measures might also lead to recall bias in reporting. Finally, we cannot generalize our findings to the overall LC and HNC patient and caregiver population because the focus is on medically underserved LC and HNC cancer patients and caregivers.

G. Data Analysis Plan: An individual-level RCT design will assess the effects of the *stepped care intervention* condition compared to *enhanced usual care* condition on distress and adaptive coping skills.

Sample size and power analysis: We estimated minimum effect sizes detectable for different power specifications for various sample sizes. Our target sample size for analyses is 290 patients and 290 caregivers (145 per arm) but we will recruit an initial sample of 222 patients and 222 caregivers (222 per arm) to allow for variability due to 24-34% attrition, based on attrition rates in meta-analyses [88] and in our studies.[57, 59] If we had a smaller number of participants or if attrition was higher, we would need a minimum of 110 dyads per arm to still be able to detect small to moderate effect sizes. Power is assumed to detect a time by treatment interaction within the proposed repeated measures design. Correlation of measures across time points (rho) was specified as moderate (.4), although sensitivity analyses examined the minimum detectable effect size at alternative specifications of rho and still allow small to moderate effects. Power calculations are for 3 outcomes through a Bonferroni reduction of the significance level to alpha = 0.05/3 = 0.0167. The study is designed to minimize contamination between intervention and control groups (e.g., randomizing both patients and their caregivers to the same group, referrals based on usual care practices). Nevertheless, based on Torgerson, we conservatively powered the study to detect a smaller effect than anticipated in the event of potential contamination. [89]

Analysis approach: Using an intent-to-treat (ITT) approach, primary and secondary outcomes will be analyzed with *linear mixed models* comparing the two groups (*stepped care intervention*, *usual care*) in patients and caregivers separately.

Data aggregation, distributional assumptions, missing data, and attrition: Maximum likelihood techniques will include participants with incomplete data without need for imputation. This technique is robust under certain conditions such that group comparisons will not be biased as long as missing data is ignorable. [90, 91] In addition, we will conduct sensitivity analyses to examine the effect of departures from key assumptions (e.g., similarity between groups) made in the main analysis and to help determine effects of missing data.[92, 93] This approach will allow us to determine whether the significance of the main analysis was maintained in all sensitivity analyses or was changed in a limited or large number of sensitivity analyses. If this is the case, then separate analyses of only those participants who complete the study will be conducted. To prevent missing data, participants will be administered the measures by research assistants trained on their proper administration. Such an approach is more appropriate for low-literacy populations and maximizes the completion of the measures. During the course of the trial, monthly reports will be generated summarizing recruitment/accrual and completeness of follow-up to allow collaborating sites to proactively follow-up with participants in a timely manner.

Verification of Randomization, Inclusion of Covariates, and Stratification: Preliminary analyses will check for baseline differences between groups. By using a RCT, we seek to have groups that will be as similar as possible, even in terms of unknown covariates, allowing us to isolate the effect of the intervention.

Should differences remain, we will co-vary variables that are correlated with the outcome and that differ by group. Because we are recruiting from four sites, we will verify that site has no impact on outcomes, either as a main effect or through interactions with treatment. Given block randomization, no differences are expected, particularly no differences in treatment response by site, though we are powered to detect differences between the four sites as low as f=.18 (Cohen's *d* = .36). In addition to site, responses to the intervention may be further stratified by tumor site (LC vs. HNC) or stage of diagnosis; thus, we will use a block randomization and adjust for imbalance by these variables. We will introduce *fixed effects* to account for stratified randomization in our primary analysis.

Analytic Strategy: Primary and secondary outcomes will be analyzed with linear mixed models comparing the two groups (*stepped care intervention*, *enhanced usual care*) in patients and caregivers separately. An alpha level of 0.05 (alpha = 0.05/3 for primary outcomes) will be used to evaluate the a priori planned comparisons. Two-tailed tests will help to detect differences between groups. The study is powered for testing the hypothesis of no group differences in change over the four time points. The software SAS PROC MIXED will be used. [94] For hypotheses addressing group differences for patients and separately for caregivers, outcomes will be evaluated with the same design: 2 groups (*stepped care intervention*, *enhanced usual care*) over 4 times (prior to randomization, 6 weeks, 3 months, 6 months). Mixed models will specify group and time and their interaction as fixed effects and subject as a random effect, where subject is assumed independently normally distributed with mean 0 and variance independent of the random errors. A significant group by time interaction is hypothesized, where those in the *stepped care intervention* are expected to improve to a greater degree than those in the enhanced usual care group. Planned comparisons of group differences at each time point will be conducted in the event of a significant interaction effect. In analyses of caregivers, the model of distress will include the caregiver's age and gender as covariates, as they have been found to be related to their distress; we will also investigate inclusion of patient distress, physical and QoL as covariates. The patient model of distress will include no *a priori* covariates, but we will explore inclusion of caregiver distress.

Heterogeneous Treatment Effects: To assess how the heterogeneity of the sample may impact treatment effects, a descriptive analysis will be conducted to estimate treatment effects with *standard errors* for important subgroups determined by levels of sex, ethnicity, tumor site (LC vs. HNC), stage (I-II vs. III-IV), hospital site and primary language (English vs. Spanish). Analyses will be based on mixed models for each subgroup. A second analysis will add each factor separately to mixed models for the entire sample. We plan to report on the pre-specified analyses and any post-hoc analyses of subgroups and outcomes analyzed to contribute to the trial's utility and interpretability for implementation and dissemination.

H. Summary of Knowledge to be Gained

Participating in an intervention that improves symptoms of distress (depression and anxiety) may help patients and their caregivers benefit from much needed assistance compared to not receiving support. By comparing the *stepped-care intervention* to usual care practices, the information gleaned from the results would demonstrate whether or not an evidence-based intervention targeted to patients' and caregivers' mental health needs would produce better patient-centered outcomes than usual care. Any temporary discomfort or time spent during the intervention is considered minimal compared to how the information gained from the study could affect future underserved LC and HNC patients. If successful and scalable, the study would not only improve access and services for underserved LC and HNC patients, but it would contribute information on effective interventions to reduce health disparities.

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